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Rios (43) **Pub. Date: Mar. 25, 2004**

(54) **METHOD FOR THE DEVELOPMENT OF AN HIV VACCINE**

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(21) Appl. No.: **10/667,534**

(22) Filed: **Sep. 22, 2003**

Related U.S. Application Data

(63) Continuation of application No. 10/331,685, filed on Dec. 30, 2002, now Pat. No. 6,649,410, which is a continuation of application No. 09/638,833, filed on Aug. 14, 2000, now Pat. No. 6,503,753, which is a continuation-in-part of application No. PCT/US99/03217, filed on Feb. 12, 1999. Continuation-in-part of application No. 10/140,356, filed on May 6, 2002, now Pat. No. 6,653,130, which is a continuation of application No. 09/249,391, filed on Feb. 12, 1999, now Pat. No. 6,383,806.

(60) Provisional application No. 60/074,646, filed on Feb. 13, 1998. Provisional application No. 60/074,646, filed on Feb. 13, 1998.

Publication Classification

(51) **Int. Cl.**[7] **A61K 48/00**

(52) **U.S. Cl.** **424/93.2**

(57) **ABSTRACT**

Human immunodeficiency virus (HIV) comprising reverse transcriptase inactivated by photoinactivation. The inactivated virus may be more safely handled, stored, and analyzed, used in diagnostic procedures and kits, and may be used as an immunogen to evoke an immune response. The immune response may protect an individual from challenges with live virus. Alternatively, the inactivated HIV particles may be used to augment the immune response to HIV in an infected individual.

PAGES TO SPEC

PHOTOINACTIVATION

10/667,534

Listing of Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1-38, 51-56 canceled.

39-50

1.-38. (Canceled)

39-47 are [illegible]

39. (Currently Amended) The method of claim [[38]] 48, wherein said one or more compounds that binds said reverse transcriptase is an azido-labeled compound.

40. (Previously Presented) The method of claim 39, wherein said azido-labeled compound is azido dipyrodiazepinona or *N*-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

41. (Previously Presented) The method of claim 39, wherein said azido-labeled compound is *N*-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

42. (Currently Amended) The method of claim [[38]] 48, wherein the irradiation is with UV light.

43. (Currently Amended) The method of claim [[38]] 48, wherein reverse transcriptase is comprised in an HIV particle.

44. (Previously Presented) The method of claim 43, wherein said HIV particle is HIV-1.

45. (Previously Presented) The method of claim 44, wherein said HIV-1 is Group M or Group O.

46. (Previously Presented) The method of claim 45, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

47. (Previously Presented) The method of claim 45, wherein said Group M particles are clade B particles.

48. (Currently Amended) ~~The method of claim 38, further~~ A method comprising:

obtaining a reverse transcriptase that has been inactivated by binding said reverse transcriptase with one or more compounds and then irradiating said reverse transcriptase; and

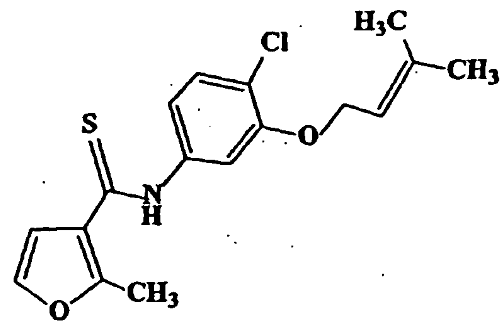
administering the inactivated reverse transcriptase to a subject.

49. (Currently Amended) The method of claim 48, wherein the subject [[in]] is human.

50. (Previously Presented) The method of claim 49, further defined as a method of vaccination.

51.-56. (Canceled)

exposure to ultraviolet light, transform into highly reactive nitrenes capable of inserting into proximal covalent bonds of the HIV-1 reverse transcriptase enzyme structure.



Structure of UC781™

5.2 EXAMPLE 2 – INACTIVATION OF HIV PARTICLES AND HIV-INFECTED CELLS

The inactivation of HIV can be accomplished by taking advantage of compounds that bind the HIV reverse transcriptase with a high degree of specificity. Using the technique of photolabeling, a compound with high specific affinity for the HIV-1 reverse transcriptase can then be turned into an "active" moiety which will produce an irreversible inactivation of the reverse transcriptase upon exposure to ultraviolet light irradiation. This inactivation, in the case of the compounds already described and known to have this effect, meets the requirement of being specific for the reverse transcriptase of HIV-1. That is, their labeling and photoactivation is not accompanied by the alteration of any other component of the viral particle than the reverse transcriptase of HIV-1. That is an important element of this invention since the irreversible inactivation of HIV-1 reverse transcriptase will lead to non-infectious particles of HIV-1 with a natural antigenic structure which should behave as the infectious particles of HIV-1 insofar as their capacity for stimulation of an effective immune response. There are many compounds that can be used for the purpose of photolabeling inactivation of the HIV-1 reverse transcriptase and include UC781™ thiocarboxanilide, UC781™ azidothiocarboxanilide, and azido dipyridodiazepinona.

aldehydes, β-propiolactone, psoralin and UV light, and others including detergents. Many of these methods alter the conformation of the virus thereby altering the specificity of the immune response to the virus. Even gamma radiation may require the additional use of protective compounds to help preserve viral protein integrity, as disclosed in U.S. Patent 6,017,543. Photoinactivation of HIV using psoralin and UV light does not alter the conformation of the virus, but it is an inefficient method of inactivation. Therefore, more efficient methods of inactivation that do not affect the conformation of the viral immunogen would be ideal for use in the production of an HIV vaccine.

2.0 SUMMARY

The prior art is devoid of HIV vaccines, HIV immunogens, and HIV viral particles created using an efficient method of inactivating HIV without causing deformation of the viral particle. The viral particles of the present invention are produced using efficient methods of inactivation that do not alter the conformation of the virus to the same extent as other inactivation methods. Moreover, the seriousness of the risk of HIV infection in those working with the virus or infected hosts or tissues dictates that non-infective virions must be inactivated in a highly efficient manner. Such non-infective virions are provided by the present invention. The photoinactivated viral particles themselves are of use in the preparation of isolated viral components. The methods of the present invention provide for the inactivation of HIV as a step in reducing the risk of HIV infection to those who work with the virus in various stages of HIV research, including virus particle isolation and analysis.

The viral particles of the present invention mimic infectious HIV particles but do not cause infection (*i.e.*, establishment of a perpetuation of HIV within the recipient host due to incorporation of HIV into the genome of cells within that host) and may be used as immunogens in a vaccine or in the development of effective treatments of HIV infection. Non-infectious HIV particles are useful not only in vaccination, but also in diagnosis, manipulation, and development of treatments for HIV infection. HIV particles rendered non-infective by photoinactivation may be used as an immunogen for making antibodies,

or screening for antibody-like binding compounds that recognize and bind to native HIV particles. These antibodies and other compounds provide means for accurate identification , quantification, and monitoring of HIV particles and infection. These uses and techniques are particularly disclosed in U.S. Patents 6,080,408 and 5,919,458, both of which are incorporated herein by reference.

The use of an azido dipyrodiazepinona and an azido thiocarboxanilide (azido UC781™), azido-labeled compounds shown to bind and inactivate RT, permits the generation of non-infectious particles of HIV by inactivating the HIV RT upon exposure of infectious particles to either compound followed by irradiation with ultraviolet light. The effective inactivation of HIV RT by the methods described herein allows the production of non-infectious particles of HIV. These non-infectious particles of HIV have the capacity of eliciting an effective cell mediated and antibody mediated immune response which is protective against infection by HIV. The inactivated HIV particles of the present invention preserve the antigenic composition of infectious wild-type HIV particles and thereby facilitate the dendritic cell-mediated processing and presentation of HIV particle-derived antigens to T cells. The inactivated HIV particles are effective immunogens.

The application of this methodology to different strains of HIV may allow the production of a polyvalent vaccine (NIIPAV or NON-Infectious Immunogenic Polyvalent AIDS Vaccine). The inactivated HIV particles of the present invention upon binding to CD4 receptors will expose epitopes which may elicit broad immunogenic responses capable of inhibiting the infectivity of diverse types of HIV from different clades. Thus the exposure of the immune system to a single type of inactivated particle of the present invention may protect against infection by multiple types of HIV.

One aspect of the present invention is a composition comprising an HIV particle in which the RT is inactivated. The composition may further comprise a pharmaceutically-acceptable excipient. The present invention contemplates that the HIV

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E3          5 -->  RIOS ADAN/IN
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E8          1      RIOS ANTONIO SANTIAGO/IN
E9          1      RIOS ARISTEO III/IN
E10         4      RIOS ARTURO M/IN
E11         1      RIOS AUGUSTO/IN
E12         1      RIOS AURELIO MARQUEZ/IN

=> s e3
L1          5 "RIOS ADAN"/IN

=> s l1 and (RT or reverse transcriptase)
         72574 RT
        564540 REVERSE
         33629 TRANSCRIPTASE
         33385 REVERSE TRANSCRIPTASE
                 (REVERSE(W)TRANSCRIPTASE)
L2          5 L1 AND (RT OR REVERSE TRANSCRIPTASE)

=> d l2,cbib,clm,1-5

L2   ANSWER 1 OF 5  USPATFULL on STN
2004:76153 Method for the development of an HIV vaccine.
    Rios, Adan, Sugar Land, TX, UNITED STATES
    US 2004057930 A1 20040325
    APPLICATION: US 2003-667534  A1  20030922 (10)
    PRIORITY: US 1998-74646P  19980213 (60)
    US 1998-74646P  19980213 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A composition comprising an HIV particle comprising inactivated
       reverse transcriptase.

       2. The composition of claim 1, further comprising a pharmaceutically-
       acceptable excipient.

       3. The composition of claim 1, wherein said HIV particle is HIV-1.

       4. The composition of claim 3, wherein said HIV-1 is Group M or Group O.

       5. The composition of claim 4, wherein said Group M are selected from
       the group consisting of clade A, clade B, clade C, clade D, clade E,
       clade F, clade G, clade H, and clade I.
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6. The composition of claim 4, wherein said Group M particles are clade B particles.

7. The composition of claim 1, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and irradiating said HIV particles comprising **reverse transcriptase** bound by said one or more compounds with UV light.

8. The composition of claim 7, wherein said binding of said **reverse transcriptase** with one or more compounds is irreversible.

9. The composition of claim 7, wherein said compounds are azido-labeled compounds.

10. The composition of claim 9, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC781.TM..

11. The composition of claim 10, wherein said azido-labeled compound is azido-UC781.TM..

12. The composition of claim 7, wherein said inactivation comprises contacting said HIV particle with an effective amount of UC781.TM..

13. A method of invoking an immune response in an animal which comprises administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an HIV particle comprising inactivated **reverse transcriptase**.

14. The method of claim 13, wherein said immune response is a cellular response

15. The method of claim 13, wherein said immune response is a humoral response.

16. The method of claim 15, wherein said cellular response comprises CD8+ T cells.

17. The method of claim 15, wherein said cellular response comprises CD4+ T cells.

18. The method of claim 13, wherein said animal is a mammal.

19. The method of claim 18, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

20. The method of claim 18, wherein said mammal is human.

21. The method of claim 13, wherein said animal is HIV-negative.

22. The method of claim 13, wherein said animal is HIV-positive.

23. A method of delaying the onset of AIDS in an animal exposed to infectious HIV which comprises administering to said animal one or more inoculations of the composition of claim 1.

24. The method of claim 23, wherein said animal is a mammal.

25. The method of claim 24, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

26. The method of claim 24, wherein said mammal is a human.

27. The method of claim 23, wherein said animal is HIV-negative at the time of administration of the composition of claim 1.

28. The method of claim 23, wherein said animal is HIV-positive at the time of administration of the composition of claim 1.

29. A method of making an HIV particle comprising an inactive **reverse transcriptase** comprising: a) obtaining an IV particle comprising **reverse transcriptase**; b) obtaining a compound capable of binding **reverse transcriptase**; c) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and d) irradiating said HIV particle.

30. The method of claim 29, wherein said HIV particle is HIV-1.

31. The method of claim 30, wherein said HIV-1 is Group M or Group O.

32. The method of claim 31, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

33. The method of claim 31, wherein said Group M particles are lade B particles.

34. The method of claim 29, wherein said compound is an azido-labeled compound.

35. The method of claim 34, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC78114.

36. The composition of claim 35, wherein said azido-labeled compound is azido-UC781.TM..

37. A method of preparing a composition comprising: a) obtaining an HIV particle comprising an inactive **reverse transcriptase** comprising: i) obtaining an HIV particle comprising **reverse transcriptase**; ii) obtaining a compound capable of binding **reverse transcriptase**; iii) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and iv) irradiating said HIV particle; and b) combining said particle into a pharmaceutically acceptable excipient.

L2 ANSWER 2 OF 5 USPATFULL on STN
2003:187414 Method for the development of an HIV vaccine.
Rios, Adan, Sugar Lano, TX, UNITED STATES
US 2003129200 A1 20030710
APPLICATION: US 2002-140356 A1 20020506 (10)
PRIORITY: US 1998-74646P 19980213 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A composition comprising an HIV particle comprising inactivated **reverse transcriptase**.

2. The composition of claim 1, further comprising a pharmaceutically-acceptable excipient.

3. The composition of claim 1, wherein said HIV particle is HIV-1.

4. The composition of claim 3, wherein said HIV-1 is Group M or Group O.

5. The composition of claim 4, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

6. The composition of claim 4, wherein said Group M particles are clade B particles.

7. The composition of claim 1, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and irradiating said HIV particles comprising **reverse transcriptase** bound by said one or more compounds with UV light.

8. The composition of claim 7, wherein said binding of said **reverse transcriptase** with one or more compounds is irreversible.

9. The composition of claim 7, wherein said compounds are azido-labeled compounds.

10. The composition of claim 9, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC781.TM..

11. The composition of claim 10, wherein said azido-labeled compound is azido-UC781.TM..

12. The composition of claim 7, wherein said inactivation comprises contacting said HIV particle with an effective amount of UC781.TM..

13. A method of invoking an immune response in an animal which comprises administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an HIV particle comprising inactivated **reverse transcriptase**.

14. The method of claim 13, wherein said immune response is a cellular response

15. The method of claim 13, wherein said immune response is a humoral response.

16. The method of claim 15, wherein said cellular response comprises CD8+ T cells.

17. The method of claim 15, wherein said cellular response comprises CD4+ T cells.

18. The method of claim 13, wherein said animal is a mammal.

19. The method of claim 18, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

20. The method of claim 18, wherein said mammal is human.

21. The method of claim 13, wherein said animal is HIV-negative.

22. The method of claim 13, wherein said animal is HIV-positive.

23. A method of delaying the onset of AIDS in an animal exposed to infectious HIV which comprises administering to said animal one or more inoculations of the composition of claim 1.

24. The method of claim 23, wherein said animal is a mammal.

25. The method of claim 24, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

26. The method of claim 24, wherein said mammal is a human.

27. The method of claim 23, wherein said animal is HIV-negative at the time of administration of the composition of claim 1.

28. The method of claim 23, wherein said animal is HIV-positive at the time of administration of the composition of claim 1.

29. A method of making an HIV particle comprising an inactive **reverse transcriptase** comprising: a) obtaining an HIV particle comprising **reverse transcriptase**; b) obtaining a compound capable of binding **reverse transcriptase**; c) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; d) irradiating said HIV particle

30. The method of claim 29, wherein said HIV particle is HIV-1.

31. The method of claim 30, wherein said HIV-1 is Group M or Group O.

32. The method of claim 31, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

33. The method of claim 31, wherein said Group M particles are lade B particles.

34. The method of claim 29, wherein said compound is an azido-labeled compound.

35. The method of claim 34, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC781.TM..

36. The composition of claim 35, wherein said azido-labeled compound is azido-UC781.TM..

37. A method of preparing a composition comprising: a) obtaining an HIV particle comprising an inactive **reverse transcriptase** comprising: i) obtaining an HIV particle comprising **reverse transcriptase**; ii) obtaining a compound capable of binding **reverse transcriptase**; iii) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and iv) irradiating said HIV particle; b) combining said particle into a pharmaceutically acceptable excipient.

L2 ANSWER 3 OF 5 USPATFULL on STN
2003:152345 Method for the development of an HIV vaccine.
Rios, Adan, Sugar Land, TX, UNITED STATES
US 2003104011 A1 20030605
APPLICATION: US 2002-331685 A1 20021230 (10)
PRIORITY: US 1998-74646P 19980213 (60)
US 1998-74646P 19980213 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition comprising an HIV particle comprising inactivated **reverse transcriptase**.

2. The composition of claim 1, further comprising a pharmaceutically-acceptable excipient.

3. The composition of claim 1, wherein said HIV particle is HIV-1.

4. The composition of claim 3, wherein said HIV-1 is Group M or Group O.

5. The composition of claim 4, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

6. The composition of claim 4, wherein said Group M particles are clade B particles.

7. The composition of claim 1, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and irradiating said HIV particles comprising **reverse transcriptase** bound by said one or more compounds with UV light.

8. The composition of claim 7, wherein said binding of said **reverse transcriptase** with one or more compounds is irreversible.

9. The composition of claim 7, wherein said compounds are azido-labeled compounds.

10. The composition of claim 9, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC781.TM..

11. The composition of claim 10, wherein said azido-labeled compound is azido-UC781.TM..

12. The composition of claim 7, wherein said inactivation comprises contacting said HIV particle with an effective amount of UC781.TM..

13. A method of invoking an immune response in an animal which comprises administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an HIV particle comprising inactivated **reverse transcriptase**.

14. The method of claim 13, wherein said immune response is a cellular response

15. The method of claim 13, wherein said immune response is a humoral response.

16. The method of claim 15, wherein said cellular response comprises CD8+ T cells.

17. The method of claim 15, wherein said cellular response comprises CD4+ T cells.

18. The method of claim 13, wherein said animal is a mammal.

19. The method of claim 18, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

20. The method of claim 18, wherein said mammal is human.

21. The method of claim 13, wherein said animal is HIV-negative.

22. The method of claim 13, wherein said animal is HIV-positive.

23. A method of delaying the onset of AIDS in an animal exposed to infectious HIV which comprises administering to said animal one or more inoculations of the composition of claim 1.

24. The method of claim 23, wherein said animal is a mammal.

25. The method of claim 24, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

26. The method of claim 24, wherein said mammal is a human.

27. The method of claim 23, wherein said animal is HIV-negative at the time of administration of the composition of claim 1.

28. The method of claim 23, wherein said animal is HIV-positive at the time of administration of the composition of claim 1.

29. A method of making an HIV particle comprising an inactive **reverse transcriptase** comprising: a) obtaining an HIV particle comprising **reverse transcriptase**; b) obtaining a compound capable of binding **reverse transcriptase**; c) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and d) irradiating said HIV particle.

30. The method of claim 29, wherein said HIV particle is HIV-1.

31. The method of claim 30, wherein said HIV-1 is Group M or Group O.

32. The method of claim 31, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

33. The method of claim 31, wherein said Group M particles are clade B particles.

34. The method of claim 29, wherein said compound is an azido-labeled compound.

35. The method of claim 34, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-UC781.TM..

36. The composition of claim 35, wherein said azido-labeled compound is azido-UC781.TM..

37. A method of preparing a composition comprising: a) obtaining an HIV particle comprising an inactive **reverse transcriptase** comprising: i) obtaining an HIV particle comprising **reverse transcriptase**; ii) obtaining a compound capable of binding **reverse transcriptase**; iii) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and iv) irradiating said HIV particle; and b) combining said particle into a pharmaceutically acceptable excipient.

L2 ANSWER 4 OF 5 USPATFULL on STN
2003:6824 Method for the development of an HIV vaccine.
Rios, Adan, 4007 Shallow Pond Ct., Sugar Land, TX, United States 77479
US 6503753 B1 20030107
APPLICATION: US 2000-638833 20000814 (9)
PRIORITY: US 1998-74646P 19980213 (60)

DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A composition comprising an HIV particle comprising inactivated **reverse transcriptase**.

2. The composition of claim 1, further comprising a pharmaceutically-acceptable excipient.

3. The composition of claim 1, wherein said HIV particle is HIV-1.

4. The composition of claim 3, wherein said HIV-1 is Group M or Group O.

5. The composition of claim 4, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

6. The composition of claim 4, wherein said Group M particles are clade B particles.

7. The composition of claim 1, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and irradiating said HIV particles comprising **reverse transcriptase** bound by said one or more compounds with UV light.

8. The composition of claim 7, wherein said binding of said **reverse transcriptase** with one or more compounds is irreversible.

9. The composition of claim 7, wherein said compounds are azido-labeled compounds.

10. The composition of claim 9, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

11. The composition of claim 10, wherein said azido-labeled compound is azido-N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

12. The composition of claim 7, wherein said inactivation comprises contacting said HIV particle with an effective amount of N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

13. A method of making an HIV particle comprising an inactive **reverse transcriptase** comprising: a) obtaining an HIV particle comprising **reverse transcriptase**; b) obtaining a compound capable of binding **reverse transcriptase**; c) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and d) irradiating said HIV particle.

14. The method of claim 13, wherein said HIV particle is HIV-1.

15. The method of claim 14, wherein said HIV-1 is Group M or Group O.

16. The method of claim 15, wherein said Group M are selected from the group consisting of clade A, clade B, clade C, clade D, clade E, clade F, clade G, clade H, and clade I.

17. The method of claim 15, wherein said Group M particles are clade B particles.

18. The method of claim 13, wherein said compound is an azido-labeled compound.

19. The method of claim 18, wherein said azido-labeled compound is azido dipyrodiazepinona or azido-N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

20. The composition of claim 19, wherein said azido-labeled compound is azido-N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

21. A method of preparing a composition comprising: a) obtaining an HIV particle comprising an inactive **reverse transcriptase** comprising: i) obtaining an HIV particle comprising **reverse transcriptase**; ii) obtaining a compound capable of binding **reverse transcriptase**; iii) contacting said HIV particle with said compound such that said compound binds said **reverse transcriptase**; and iv) irradiating said HIV particle; and b) combining said particle into a pharmaceutically acceptable excipient.

L2 ANSWER 5 OF 5 USPATFULL on STN
2002:102318 Method for the development of an HIV vaccine.
Rios, Adan, 4007 Shallow Pond Ct., Sugar Land, TX, United States 77479
US 6383806 B1 20020507
APPLICATION: US 1999-249391 19990212 (9)
PRIORITY: US 1998-74646P 19980213 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of invoking an immune response in an animal which comprises administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an HIV particle comprising inactivated **reverse transcriptase**, wherein said **reverse transcriptase** has been inactivated by a method comprising binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and then irradiating said HIV particles with UV light.

2. The method of claim 1, wherein said immune response is a cellular response.

3. The method of claim 1, wherein said immune response is a humoral response.

4. The method of claim 2, wherein said cellular response comprises CD8+ T cells.

5. The method of claim 2, wherein said cellular response comprises CD4+ T cells.

6. The method of claim 1, wherein said animal is a mammal.

7. The method of claim 1, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

8. The method of claim 6, wherein said mammal is human.

9. The method of claim 1, wherein said animal is HIV-negative.

10. The method of claim 1, wherein said animal is HIV-positive.

11. The method of claim 1, wherein said compound is an azido-labeled compound.

12. The method of claim 11, wherein said azido-labeled compound is azido dipyrodiazepinona or N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

13. The method of claim 12, wherein said azido-labeled compound is N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

14. A method of invoking an immune response in an animal which comprises: administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an HIV particle comprising inactivated **reverse transcriptase**, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with at least one compound that binds said **reverse transcriptase** and then irradiating said HIV particle with UV light.

15. The method of claim 14, wherein said compound is an azido-labeled compound.

16. The method of claim 15, wherein said azido-labeled compound is azido dipyrodiazepinona or N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

17. The method of claim 16, wherein said azido-labeled compound is N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

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=> file wpids
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    14.29      14.50

FILE 'WPIDS' ENTERED AT 04:13:32 ON 02 OCT 2006
COPYRIGHT (C) 2006 THE THOMSON CORPORATION

FILE LAST UPDATED:          27 SEP 2006      <20060927/UP>
MOST RECENT DERWENT UPDATE:     200662        <200662/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
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http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

=> e rios a/in
E1          13     RIORDAN W J/IN
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E2          2      RIORDON B B/IN
E3          4 -->  RIOS A/IN
E4          1      RIOS A A/IN
E5          1      RIOS A C/IN
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E7          1      RIOS A S/IN
E8          1      RIOS AGUILAR G/IN
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E12         1      RIOS B J/IN

=> s e3-e11
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            1 "RIOS A C"/IN
            5 "RIOS A M"/IN
            1 "RIOS A S"/IN
            1 "RIOS AGUILAR G"/IN
            2 "RIOS ALEMAN D"/IN
            4 "RIOS ALEMAN D E"/IN
            2 "RIOS ALEMAN E"/IN
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              OR "RIOS A S"/IN OR "RIOS AGUILAR G"/IN OR "RIOS ALEMAN D"/IN
             OR "RIOS ALEMAN D E"/IN OR "RIOS ALEMAN E"/IN)

=> s l3 and (RT or reverse transcriptase)
         5394 RT
       181916 REVERSE
         3294 TRANSCRIPTASE
         3221 REVERSE TRANSCRIPTASE
                (REVERSE(W)TRANSCRIPTASE)
L4          1 L3 AND (RT OR REVERSE TRANSCRIPTASE)

=> d l4,bib,ab

L4    ANSWER 1 OF 1  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN    1999-508644 [42]    WPIDS
DNC   C1999-148624
TI    Human immunodeficiency virus vaccine  - comprises an HIV particle
      comprising inactivated reverse transcriptase.
DC    B04 D16
IN    RIOS, A
PA    (RIOS-I) RIOS A
CYC   85
PI    WO 9941360       A1 19990819 (199942)* EN   50
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             OA PT SD SE SZ UG ZW
          W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD
             GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
             MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
             UA UG US UZ VN YU ZW
      AU 9932937       A  19990830 (200003)
      EP 1056838       A1 20001206 (200064)  EN
          R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
      US 6383806       B1 20020507 (200235)
      US 6503753       B1 20030107 (200306)
      US 2003104011    A1 20030605 (200339)
      US 2003129200    A1 20030710 (200347)
      AU 764938        B  20030904 (200368)
      US 6649410       B2 20031118 (200376)
```

US 6653130 B2 20031125 (200378)
US 2004057930 A1 20040325 (200422)

ADT WO 9941360 A1 WO 1999-US3217 19990212; AU 9932937 A AU 1999-32937 19990212; EP 1056838 A1 EP 1999-932507 19990212, WO 1999-US3217 19990212; US 6383806 B1 Provisional US 1998-74646P 19980213, US 1999-249391 19990212; US 6503753 B1 Provisional US 1998-74646P 19980213, CIP of WO 1999-US3217 19990212, US 2000-638833 20000814; US 2003104011 A1 Provisional US 1998-74646P 19980213, CIP of US 1999-249391 19990212, CIP of WO 1999-US3217 19990212, Cont of US 2000-638833 20000814, US 2002-331685 20021230; US 2003129200 A1 Provisional US 1998-74646P 19980213, Cont of US 1999-249391 19990212, US 2002-140356 20020506; AU 764938 B AU 1999-32937 19990212; US 6649410 B2 Provisional US 1998-74646P 19980213, Provisional US 1998-74686P 19980213, CIP of US 1999-249391 19990212, CIP of WO 1999-US3217 19990212, Cont of US 2000-638833 20000814, US 2002-331685 20021230; US 6653130 B2 Provisional US 1998-74646P 19980213, Cont of US 1999-249391 19990212, US 2002-140356 20020506; US 2004057930 A1 Provisional US 1998-74646P 19980213, Cont of US 1999-249391 19990212, CIP of WO 1999-US3217 19990212, Cont of US 2000-638833 20000814, CIP of US 2002-140356 20020506, Cont of US 2002-331685 20021230, US 2003-667534 20030922

FDT AU 9932937 A Based on WO 9941360; EP 1056838 A1 Based on WO 9941360; US 2003104011 A1 CIP of US 6383806, Cont of US 6503753; US 2003129200 A1 Cont of US 6383806; AU 764938 B Previous Publ. AU 9932937, Based on WO 9941360; US 6649410 B2 CIP of US 6383806, Cont of US 6503753; US 6653130 B2 Cont of US 6383806; US 2004057930 A1 Cont of US 6383806, Cont of US 6503753, Cont of US 6649410, CIP of US 6653130

PRAI US 1998-74646P 19980213; US 1999-249391 19990212;
US 2000-638833 20000814; US 2002-331685 20021230;
US 2002-140356 20020506; US 1998-74686P 19980213;
US 2003-667534 20030922

AB WO 9941360 A UPAB: 19991020

NOVELTY - A composition (I) comprising an HIV particle comprising inactivated **reverse transcriptase** (RTase) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) preparation of an HIV particle comprising an inactive RTase by: (a) obtaining an HIV particle comprising RTase; (b) obtaining a compound capable of binding RTase; (c) contacting the HIV particle with the compound such that the compound binds the RTase, and (d) irradiating the HIV particle; and (2) preparing a composition by: (a) obtaining an HIV particle comprising inactive RTase performed as in (1a)-(1d), and (b) combining the particle into an excipient.

USE - (I) may be administered to an mammal to invoke an immune response or to delay the onset of AIDS in the mammal exposed to infectious HIV (all claimed). The immune response elicited is a cellular response or a humoral response and the cellular response comprises CD8+ T cells or CD4+ T cells. The immune response provides protection from an HIV challenge and/or assists the HIV infected individual in controlling the viral replication.

ADVANTAGE - Previously used HIV vaccines were produced using methods that cause deformation of HIV particles therefore altering the specificity of the immune response. The vaccine produced by the new methods uses efficient methods of HIV inactivation that do not alter the viral conformation to the same extent as the previous inactivation methods. Therefore the new vaccine mimics infectious HIV particles but does not cause infection (i.e. establishment of perpetuation of HIV within the recipient host due to incorporation of HIV into the cell genome of the host). The non-infectious particles produced have the capacity of eliciting an effective cell and antibody mediated immune response which is protective against HIV infection.

Dwg.0/1

```
=> file medline
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    12.39      26.89

FILE 'MEDLINE' ENTERED AT 04:14:45 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e rios a/au
E1           1      RIORDON T P/AU
E2           2      RIOS/AU
E3         259 -->  RIOS A/AU
E4           4      RIOS A A/AU
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E8           1      RIOS A MARIA/AU
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=> s e3
L5         259 "RIOS A"/AU

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L6           2 L5 AND (RT OR REVERSE TRANSCRIPTASE)

=> d l6,cbib,ab,1-2

L6   ANSWER 1 OF 2     MEDLINE on STN
87312033.    PubMed ID: 3650339.    Suramin therapy in AIDS and related
     disorders. Report of the US Suramin Working Group. Cheson B D; Levine A M;
     Mildvan D; Kaplan L D; Wolfe P; Rios A; Groopman J E; Gill P; Volberding
     P A; Poiesz B J; +. JAMA : the journal of the American Medical
     Association, (1987 Sep 11) Vol. 258, No. 10, pp. 1347-51.  Journal code:
     7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.
```

AB Suramin sodium is a **reverse transcriptase** inhibitor with in vitro activity against the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS). Ninety-eight patients with AIDS manifest as opportunistic infections (n = 38), AIDS with Kaposi's sarcoma (n = 38), AIDS-related complex (n = 20), or AIDS-associated non-Hodgkin's lymphoma (NHL) (n = 2) were treated with suramin sodium at 0.5, 1.0, or 1.5 g/wk for six weeks followed by maintenance therapy with 0.5 or 1.0 g/wk. Of 72 patients who were HIV culture positive before therapy and were assessable for subsequent HIV culture 40% became culture negative during treatment, with no apparent correlation between virus recovery and serum suramin concentration. No immunologic improvement was noted. One complete clinical remission was noted in a patient with Kaposi's sarcoma and stage IV NHL. Seven minor clinical responses were also noted. Toxic reactions were generally reversible, and included fever (78%), rash (48%), malaise (43%), nausea (34%), neurologic symptoms (33%), and vomiting (20%). Suramin-induced neutropenia was noted in 26%, thrombocytopenia in 12%, a serum creatinine level of 180 mumol/L or higher (greater than or equal to 2.1 mg/dL) in 12%, liver dysfunction in 14%, and clinical and/or laboratory evidence of adrenal insufficiency in 23%. Sixteen patients died while receiving suramin or within three weeks of discontinuation of drug therapy due to infection (n = 6), hepatic failure (n = 3), pulmonary Kaposi's sarcoma (n = 2), AIDS encephalitis (n = 2), AIDS-associated NHL (n = 1), iatrogenic hemo-pneumothorax (n = 1), or pulmonary disease of uncertain etiology. Suramin as currently administered cannot be recommended as effective therapy for AIDS.

L6 ANSWER 2 OF 2 MEDLINE on STN
78070212. PubMed ID: 592852. The combined effect of radiotherapy and neuraminidase-treated tumor cells on 3-methylcholanthrene-induced fibrosarcoma. So S K; Song C W; **Rios A**; Simmons R L. Journal of surgical oncology, (1977) Vol. 9, No. 6, pp. 527-40. Journal code: 0222643. ISSN: 0022-4790. Pub. country: United States. Language: English.

AB Active immunotherapy with tumor cells treated in vitro with Vibrio cholerae neuraminidase (VCN) plus mitomycin C augments the antitumor effects of local x irradiation in the treatment of firmly established methylcholanthrene-induced fibrosarcoma, MC-43, in syngeneic C3H/HeJ female mice. In most experiments, the inhibition of tumor growth was greater when VCN-treated tumor cells were combined with local irradiation than could be achieved with VCN-treated tumor cells or local irradiation alone. Even in those experiments in which the immunotherapeutic effect of VCN-treated cells was negligible, the combination of radiotherapy and immunotherapy appeared to be greater than irradiation alone. Similarly, total permanent regression of established tumors occurred more frequently after combined therapy than after immunotherapy or radiation therapy alone.

```
=> d his

     (FILE 'HOME' ENTERED AT 04:11:15 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 04:11:30 ON 02 OCT 2006
                E RIOS ADAN/IN
L1            5 S E3
L2            5 S L1 AND (RT OR REVERSE TRANSCRIPTASE)

     FILE 'WPIDS' ENTERED AT 04:13:32 ON 02 OCT 2006
                E RIOS A/IN
L3           18 S E3-E11
L4            1 S L3 AND (RT OR REVERSE TRANSCRIPTASE)
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     FILE 'MEDLINE' ENTERED AT 04:14:45 ON 02 OCT 2006
                E RIOS A/AU
L5          259 S E3
L6            2 S L5 AND (RT OR REVERSE TRANSCRIPTASE)

=> file uspatful
COST IN U.S. DOLLARS                                   SINCE FILE      TOTAL
                                                            ENTRY    SESSION
FULL ESTIMATED COST                                          1.61      28.50

FILE 'USPATFULL' ENTERED AT 04:16:37 ON 02 OCT 2006
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


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          45383 HIV
         522505 HUMAN
          25660 IMMUNODEFICIENCY
         105701 VIRUS
          18282 HUMAN IMMUNODEFICIENCY VIRUS
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L10           8 L9 AND (REVERSE TRANSCRIPTASE)

=> d l10,cbib,clm,1-8

L10  ANSWER 1 OF 8  USPATFULL on STN
2002:140867 VIRUS VACCINES.
    SMITH, GALE EUGENE, WALLINGFORD, CT, UNITED STATES
    WILKINSON, BETHANIE E., HIGGANUM, CT, UNITED STATES
    VOZNESENSKY, ANDREI I., WEST HARTFORD, CT, UNITED STATES
    VOLVOVITZ, FRANKLIN, WOODBRIDGE, CT, UNITED STATES
    HACKETT, CRAIG S., WALLINGFORD, CT, UNITED STATES
    US 2002071848 A1 20020613
    APPLICATION: US 1999-235901  A1  19990122 (9)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
```

1. An influenza virus vaccine composition for a human being comprising an immunogenic amount of inactivated influenza virus and an immunogenic amount of a purified recombinant envelope protein from the virus, or a fragment or precursor thereof.

2. A composition according to claim 1 wherein the recombinant envelope protein is hemagglutinin.

3. A composition according to claim 2 wherein the hemagglutinin is uncleaved HA0.

4. A composition according to claim 3 wherein the hemagglutinin is produced with recombinant baculovirus vectors in lepidopteran cell cultures and extracted and purified under non-denaturing conditions to at least 90% purity.

5. A composition according to claim 1 wherein the inactivated influenza virus comprises three strains of the virus and the recombinant envelope protein comprises at least one hemagglutinin from one strain.

6. A composition according to claim 5 wherein the recombinant envelope protein comprises the corresponding hemagglutinins for each strain.

7. A composition according to claim 1 wherein the recombinant envelope protein is neuraminidase.

8. A composition according to claim 7 wherein the neuraminidase is tetrameric.

9. A composition according to claim 8 wherein the neuraminidase is produced with recombinant baculovirus vectors in lepidopteran cell cultures and extracted and purified under non-denaturing conditions to at least 90 % purity.

10. A composition according to claim 7 wherein the inactivated influenza virus comprises three strains of the virus and the recombinant envelope protein comprises at least one neuraminidase from one of the strains.

11. A composition according to claim 10 wherein the recombinant envelope protein comprises corresponding neuraminidases for each strain.

12. A composition according to claim 1 wherein the recombinant envelope protein comprises both neuraminidase and hemagglutinin.

13. A composition according to claim 10 wherein the inactivated virus component comprises three strains of the virus and the envelope protein comprises hemagglutinins for at least one of the strains and neuraminidase for at least one of the three strains.

14. A composition according to claim 1 further comprising a colony stimulating factor adjuvant.

15. A composition according to claim 14 wherein the adjuvant is granulocyte-microphage colony stimulating factor.

16. A mammalian vaccine composition comprising a combination of at least two components selected from the group consisting of an immunogenic amount of inactivated virus, an immunogenic amount of a purified recombinant envelope protein from said virus, or a fragment or precursor thereof, and an effective amount of a colony stimulating factor.

17. A composition according to claim 16 wherein the colony stimulating

factor is granulocyte-macrophage colony stimulating factor.

18. A composition according to claim 16 wherein the virus is Herpes varicella, the recombinant protein is Herpes varicella envelope glycoprotein D, and the colony stimulating factor is granulocyte-macrophage colony stimulating factor.

19. A composition according to claim 16 wherein the virus is measles virus, the colony stimulating factor is granulocyte-macrophage colony stimulating factor, and the recombinant protein is selected from the group consisting of virus envelope F protein, virus envelope G protein, virus envelope FG polyprotein, and mixtures thereof.

20. A composition according to claim 16 comprising three strains of inactivated influenza virus and hemagglutinins for each of the three strains, wherein the hemagglutinins are uncleaved HA0 produced with recombinant baculovirus vectors in lepidopteran cell cultures and extracted and purified under non-denaturing conditions to at least 90% purity.

21. A composition according to claim 16 comprising three strains of inactivated influenza virus and neuraminidase for each of the three strains, wherein the neruaminidase are tetrameric and produced with recombinant baculovirus vectors in lepidopteran cell cultures and extracted and purified under non-denaturing conditions to at least 90% purity.

22. A composition according to claim 16 wherein in the combinations are selected from the group consisting of: (a) inactivated Epstein Barr virus and recombinant virus gp340 envelope protein; (b) inactivated respiratory syncytial virus and a recombinant protein selected from the group consisting of virus envelope F protein, virus envelope G protein, virus envelope FG polyprotein, and mixtures thereof; (c) inactivated parainfluenza 3 virus and a recombinant protein selected from the group consisting of virus envelope F protein, virus envelope G protein, virus envelope FG polyprotein, and mixtures thereof; (d) inactivated Herpes simplex type 1 virus and recombinant virus envelope glycoprotein D; and (e) inactivated Herpes simplex type 2 virus and recombinant virus envelope glycoprotein D.

23. A composition according to claim 21 further comprising granulocyte-macrophage colony stimulating factor.

24. A method for immunizing a human being against a virus infection selected from the group consisting of influenza and chicken pox, comprising inoculating the human being with a vaccine composition comprising a combination of at least two components selected from the group consisting of an immunogenic amount of the respective attenuated virus causing the infection, an effective amount of a colony stimulating growth factor, and an immunogenic amount of a purified recombinant envelope protein from said virus, or fragment or precursor thereof.

25. A method according to claim 21 wherein the virus is influenza virus, the colony stimulating factor is granulocyte-macrophage colony stimulating factor, and the recombinant envelope protein is selected from the group consisting of hemagglutinin, neuraminidase, and mixtures thereof.

26. A method according to claim 24 wherein the vaccine composition comprises three strains of virus and at least one envelope protein corresponding to each strain.

L10 ANSWER 2 OF 8 USPATFULL on STN
2002:102318 Method for the development of an **HIV** vaccine.
Rios, Adan, 4007 Shallow Pond Ct., Sugar Land, TX, United States 77479
US 6383806 B1 20020507
APPLICATION: US 1999-249391 19990212 (9)
PRIORITY: US 1998-74646P 19980213 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of invoking an immune response in an animal which comprises administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an **HIV** particle comprising inactivated **reverse transcriptase**, wherein said **reverse transcriptase** has been inactivated by a method comprising binding said **reverse transcriptase** with one or more compounds that binds said **reverse transcriptase** and then irradiating said **HIV** particles with UV light.

2. The method of claim 1, wherein said immune response is a cellular response.

3. The method of claim 1, wherein said immune response is a humoral response.

4. The method of claim 2, wherein said cellular response comprises CD8+ T cells.

5. The method of claim 2, wherein said cellular response comprises CD4+ T cells.

6. The method of claim 1, wherein said animal is a mammal.

7. The method of claim 1, wherein said mammal is a PBL-SCID mouse or a SCID-hu mouse.

8. The method of claim 6, wherein said mammal is human.

9. The method of claim 1, wherein said animal is **HIV**-negative.

10. The method of claim 1, wherein said animal is **HIV**-positive.

11. The method of claim 1, wherein said compound is an azido-labeled compound.

12. The method of claim 11, wherein said azido-labeled compound is azido dipyrodiazepinona or N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

13. The method of claim 12, wherein said azido-labeled compound is N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

14. A method of invoking an immune response in an animal which comprises: administering to said animal a composition comprising a pharmaceutically-acceptable excipient and an **HIV** particle comprising inactivated **reverse transcriptase**, wherein said **reverse transcriptase** has been inactivated via binding said **reverse transcriptase** with at least one compound that binds said **reverse transcriptase** and then irradiating said **HIV** particle with UV light.

15. The method of claim 14, wherein said compound is an azido-labeled

compound.

16. The method of claim 15, wherein said azido-labeled compound is azido dipyrodiazepinona or N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

17. The method of claim 16, wherein said azido-labeled compound is N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furanocarbothiamide.

L10 ANSWER 3 OF 8 USPATFULL on STN
1999:166867 Repair-mediated process for amplifying and detecting nucleic acid sequences.
Segev, David, Moshav Bne-Rem 40, D. N. Evtah, Israel 79840
Segev, David, United States (U.S. individual)
US 6004826 19991221
APPLICATION: US 1993-155938 19931027 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A process for detecting a specific nucleic acid target molecule in a sample by amplifying the nucleic acid target molecule, the process comprising the steps of: a) treating the sample with at least two oligonucleotides for each strand of the target molecule, under hybridizing conditions, i) wherein the oligonucleotides are selected so as to be sufficiently complementary to each strand of the target molecule to hybridize therewith under the hybridizing conditions; and ii) wherein a gap of one or more bases is present between two oligonucleotides when the two oligonucleotides are hybridized to a strand of the target molecule; and iii) wherein the oligonucleotides are selected so that the gaps between them will require less than all four types of bases to fill the gaps; b) filling the gaps formed in step (a) with one or more bases complementary to the base or bases in the gaps and joining the base or bases filling the gaps to each other and to both adjacent hybridized oligonucleotides, thereby forming a joined oligonucleotide product; c) treating the hybridized joined oligonucleotide product of step (b) under denaturing conditions to separate the joined oligonucleotide products from the target molecule to produce single-stranded molecules; d) treating the single-stranded molecules produced in step (c) with an excess of at least two oligonucleotide complement pairs, under hybridizing conditions, i) wherein each oligonucleotide complement pair comprises two oligonucleotides selected so as to be sufficiently complementary to each other, to each strand of the target molecule and to the joined oligonucleotide products to hybridize therewith under the hybridizing conditions; and ii) wherein gaps of one or more bases are present between the oligonucleotides when the oligonucleotides are hybridized to each strand of the target molecule; and iii) wherein the oligonucleotides are selected so that the gaps between them will require less than all four types of bases to fill the gaps; e) filling in the gaps formed in step (d) with one or more bases complementary to the base or bases in the gaps and joining the bases filling the gaps to each other and to both adjacent hybridized oligonucleotides, thereby forming additional joined oligonucleotide products, resulting in the amplification of the target molecule; and f) detecting the joined oligonucleotide products.

2. The process of claim 1, further including step e') treating the hybridized oligonucleotides of step e) under denaturing conditions to separate the hybridized oligonucleotides and produce single-stranded molecules, wherein steps (d), (e) and (e') are repeated a desired number

of times.

3. The process of claim 1, wherein the nucleic acid target molecule is double-stranded DNA and its strands are separated before or during step (a).

4. The process of claim 1, wherein the nucleic acid target molecule is single-stranded DNA.

5. The process of claim 1, wherein the nucleic acid target molecule is single-stranded RNA.

6. The process of claim 1, wherein the oligonucleotides are oligodeoxyribonucleotides.

7. The process of claim 1, wherein the oligonucleotide complement pairs are present as a molar excess in the range of 105 to 1015 pairs per nucleic acid target molecule.

8. The process of claim 1, wherein the gaps are filled by a DNA polymerase and a DNA ligase.

9. The process of claim 8, wherein the DNA polymerase and the DNA ligase are immobilized on polymeric supports.

10. The process of claim 8, wherein the DNA polymerase is selected from the group consisting of E. coli DNA polymerase-I, Klenow fragments of E. coli DNA polymerase-I, T4 DNA polymerase, and **reverse transcriptase** and the DNA ligase is selected from the group consisting of E. coli DNA ligase and T4 DNA ligase.

11. The process of claim 8, wherein the DNA polymerase is heat stable.

12. The process of claim 8, wherein the DNA ligase is heat stable.

13. The process of claim 8, wherein the heat stable polymerase and ligase are isolated from a thermophilic bacteria.

14. The process of claim 1, wherein the oligonucleotides and/or deoxyribonucleic triphosphates are modified to be resistant to 3'→5' exonuclease activity.

15. A process for detecting a specific nucleic acid target molecule in a sample by amplifying the nucleic acid target molecule, the process comprising the steps of: a) treating the sample with at least two oligonucleotides for each strand of the target molecule, under hybridizing conditions, i) wherein the oligonucleotides are selected so as to be sufficiently complementary to each strand of the target molecule to hybridize therewith under the hybridizing conditions; and ii) wherein a gap of more than one bases is present between two oligonucleotides when the two oligonucleotides are hybridized to a strand of the target molecule; and iii) wherein the oligonucleotides are selected so that the gaps between them will require less than all four types of bases to fill the gaps; b) filling the gaps formed in step (a) with one or more bases complementary to the base or bases in the gaps and joining the base or bases filling the gaps to each other and to both adjacent hybridized oligonucleotides, thereby forming a joined oligonucleotide product; c) treating the hybridized joined oligonucleotide product of step (b) under denaturing conditions to separate the joined oligonucleotide products from the target molecule to produce single-stranded molecules; d) treating the single-stranded molecules produced in step (c) with an excess of at least two

oligonucleotide complement pairs, under hybridizing conditions, i) wherein each oligonucleotide complement pair comprises two oligonucleotides selected so as to be sufficiently complementary to each other, to each strand of the target molecule and to the joined oligonucleotide products to hybridize therewith under the hybridizing conditions; and ii) wherein gaps of more than one bases are present between the oligonucleotides when the oligonucleotides are hybridized to each strand of the target molecule; and iii) wherein the oligonucleotides are selected so that the gaps between them will require less than all four types of bases to fill the gaps; e) filling in the gaps formed in step (d) with one or more bases complementary to the base or bases in the gaps and joining the bases filling the gaps to each other and to both adjacent hybridized oligonucleotides, thereby forming additional joined oligonucleotide products, resulting in the amplification of the target molecule; and f) detecting the joined oligonucleotide products.

L10 ANSWER 4 OF 8 USPATFULL on STN
97:3821 Treatment of viral hepatitis with mismatched dsRNA.
Carter, William A., Birchrunville, PA, United States
Hemispherx Biopharma Inc., Philadelphia, PA, United States (U.S. corporation)
US 5593973 19970114
APPLICATION: US 1994-318514 19941005 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating viral hepatitis comprising administering to a person having vital hepatitis an effective amount of a mismatched double-stranded RNA of the formula rIn.r(C11-14, U)n.

2. The method of claim 1 in which the mismatched dsRNA is administered in an amount which will result in a level of from 1 to 1,000 micrograms per milliliter of the patient's body fluid.

3. The method of claim 1 in which the amount administered is 400 mg per week.

L10 ANSWER 5 OF 8 USPATFULL on STN
94:32784 Method of eradicating infectious biological contaminants.
Sieber, Fritz, Brookfield, WI, United States
Smith, Orla M., Milwaukee, WI, United States
The MCW Research Foundation, Inc., Milwaukee, WI, United States (U.S. corporation)
US 5304113 19940419
APPLICATION: US 1990-608458 19901102 (7)
DOCUMENT TYPE: Utility; Granted.
CLM What is claimed is:

1. A method for eradicating infectious pathogenic biological contaminants from body fluids outside the body prior to introduction of the decontaminated body fluids into the body of a patient, said method comprising: admixing an effective, non-toxic amount of a photoactive compound with the body fluid to product a resulting body fluid, the photoactive compound having an affinity to be selectively bound to the contaminants; passing the resulting fluid under flow conditions through a cell assembly having a predetermined flow path; and irradiating the resulting fluid in the cell assembly as same passes through the flow path with an effective level of radiation in the region of the visible spectrum, with a wavelength range above 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the

resulting fluid and exposes the photoactive-compound-bound contaminants to the radiation so as to eradicate such contaminants while maintaining the viability of said body fluids to produce viable decontaminated body fluids.

2. The eradicating method as recited in claim 1 further comprising the step of selecting a body fluid from the group consisting of whole blood, blood plasma, serum, and fluids from plasmapheresis.

3. . The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain an envelope-containing virus.

4. The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising a malarial parasite.

5. A method of extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants said method comprising: removing blood from the body of a patient infected with infectious pathogenic biological contaminants; adding to said blood, before the removal of the blood, an effective, non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; passing said treated blood through a cell assembly having a predetermined flow path; irradiating said contaminated blood admixed with photoactive compound in the cell assembly as same passes through the flow path with an effective level of radiation in the region of visible spectrum, with a wavelength range 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of components in said blood to produce a viable and decontaminated blood; and returning said viable and decontaminated blood to the patient's body.

6. The method of claim 5 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 1000 nm.

7. The eradicating method as recited in claim 5 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising an envelope-containing virus.

8. The eradicating method as recited in claim 5 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

9. The eradicating method as recited in claim 5 further comprising the step of selecting the pathogenic biological contaminants comprising a malarial parasite.

10. The eradicating method as recited in claim 5 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising a trypanosomal parasite.

11. A method for extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants, said method comprising: removing blood from the body of a patient infected with infectious pathogenic foreign biological contaminants; adding to said blood, after the removal of the blood, an effective non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; passing said treated blood through a cell assembly having a predetermined flow path; irradiating said contaminated

blood admixed with photoactive compound in the cell assembly as the same passes through the flow path with an effective level of radiation in the region of visible spectrum, with a wavelength range above 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of compounds in said blood to produce a viable and decontaminated blood; and returning said viable and decontaminated blood to the patient's body.

L10 ANSWER 6 OF 8 USPATFULL on STN
91:66432 Photodynamic viral deactivation with sapphyrins.
Matthews, J. Lester, Dallas, TX, United States
Judy, Millard M., Dallas, TX, United States
Newman, Joseph T., Dallas, TX, United States
Sogandares-Bernal, Frank, Dallas, TX, United States
Sessler, Jonathan L., Austin, TX, United States
Harriman, Anthony, Austin, TX, United States
Maiya, Bhaskar G., Hyderabad, India
Baylor Research Foundation, a nonprofit corporation of the State of Texas, Dallas, TX, United States (U.S. corporation)Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
US 5041078 19910820
APPLICATION: US 1989-454300 19891221 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of photodynamic inactivation of infectious agents, comprising: forming a mixture by adding a decaalkylsapphyrin or a dicarboxy functionalized decaalkylsapphyrin compound to a fluid comprising infectious agents; and subjecting said mixture to irradiation with light at a wavelength at or near the absorption maximum of said decaalkylsapphyrin or dicarboxy functionalized decaalkylsapphyrin compound for a time and at an intensity sufficient to inactivate said infectious agents.

2. The method of claim 1 wherein the decaalkylsapphyrin compound is 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

3. The method of claim 1 wherein the dicarboxy functionalized decaalkylsapphyrin compound is a dicarboxy-functionalized analog of 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

4. The method of claim 1 wherein the dicarboxy functionalized decaalkylsapphyrin compound is 8,17-bis(carboxymethyl)-3,12,13,22-tetraethyl-2,7,18,23-tetramethylsapphyrin.

5. The method of claim 1 wherein the wavelength is between about 600 nm and 700 nm.

6. The method of claim 1 wherein the wavelength is about 680 nm.

7. The method of claim 1 wherein the light is provided by a laser.

8. The method of claim 1 wherein the irradiation is at an intensity of from about 20 mW/cm2 to about 50 mW/cm2.

9. The method of claim 1 wherein the irradiation results in an exposure of the mixture to 10 Joules/cm2.

10. The method of claim 1 wherein the the decaalkylsapphyrin or

dicarboxy functionalized decaalkylsapphyrin compound in the mixture is at a concentration between about 4 uM and 35 uM.

11. A method of photodynamic inactivation of viruses or retroviruses, comprising: obtaining a viral or retroviral suspension in a fluid; adding a decaalkylsapphyrin or a dicarboxy functionalized decaalkylsapphyrin compound to said suspension; and irradiating said suspension with light at a wavelength at or near the visible absorption maximum of said decaalkylsapphyrin or dicarboxy functionalized decaalkylsapphyrin compound for a time and at an intensity sufficient to effect inactivation of virus or retrovirus in said suspension.

12. The method of claim 11 wherein the wavelength is 680 nm.

13. The method of claim 11 wherein the intensity sufficient to effect the inactivation is about 20 mW/cm2 to about 40 mW/cm2.

14. The method of claim 11 wherein the irradiating sufficient to effect the inactivation is in an amount of about 10 J/cm2.

15. The method of claim 11 wherein the viral or retroviral suspension comprises cytomegalovirus, hepatitis virus type B; non-A, non-B hepatitis virus, human lymphotrophic virus type 1, **human immunodeficiency virus** type 1, simian immunodeficiency virus, or herpes simplex virus type 1.

16. The method of claim 11 wherein the viral or retroviral suspension comprises a membranous enveloped virus.

17. The method of claim 11 wherein the decaalkylsapphyrin compound is 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

18. The method of claim 11 wherein the dicarboxy functionalized decaalkylsapphyrin compound is 8,17-bis(carboxymethyl)-3,12,13,22-tetraethyl-2,7,18,23-tetramethylsapphyrin.

19. The method of claim 11 wherein the fluid is blood or a blood product.

20. A method of photodynamic inactivation of enveloped viruses or retroviruses in blood, comprising: circulating virus-containing or retrovirus-containing blood through a transparent tube arranged in multiple planar loops; adding a decaalkylsapphyrin or a dicarboxy functionalized decaalkylsapphyrin compound to said circulating blood; and irradiating said circulating blood at a wavelength of about 680 nm.

21. The method of claim 20 wherein the decaalkylsapphyrin compound is 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin.

22. The method of claim 20 wherein the dicarboxy functionalized decaalkylsapphyrin compound is 8,17-bis(carboxymethyl)-3,12,13,22-tetraethyl-2,7,18,23-tetramethylsapphyrin.

23. A method of photodynamic deactivation of infectious agents in a fluid, comprising: mixing a decaalkylsapphyrin or a dicarboxy functionalized decaalkylsapphyrin compound with a fluid to be purified; irradiating said fluid at a wavelength at or near the absorption maximum of said decaalkylsapphyrin or dicarboxy functionalized decaalkylsapphyrin compound at an intensity and for a period of time sufficient to inactivate one or more infectious agents that may be present in said fluid.

24. The method of claim 23 wherein said fluid is irradiated at a wavelength of about 680 nm.

25. The method of claim 23 wherein the irradiating is at an energy of about 10 J/cm2.

26. The method of claim 23 wherein the decaalkylsapphyrin or dicarboxy functionalized decaalkylsapphyrin compound in the fluid is at a concentration of about 4 uM to about 35 uM.

27. The method of claim 23 wherein the dicarboxy functionalized decaalkylsapphyrin compound is 8,17-bis(carboxymethyl)-3,12,13,22-tetraethyl-2,7,18,23-tetramethylsapphyrin.

28. The method of claim 23 wherein the fluid is further characterized as being blood.

29. The method of claim 23 wherein the fluid is further characterized as being a blood product.

30. The method of claim 23 wherein the infectious agent is a virus or retrovirus.

31. The method of claim 30 wherein the virus or retrovirus is further characterized as having an envelope.

32. The method of claim 30 wherein the virus or retrovirus is characterized as being cytomegalovirus, hepatitis virus type B; non-A, non-B hepatitis virus, human lymphotrophic virus type 1, **human immunodeficiency virus** type 1, simian immunodeficiency virus, Epstein barr virus, or herpes simplex virus type 1.

33. The method of claim 23 wherein the infectious agent is Tympanosoma cruzi or malaria plasmodium.

L10 ANSWER 7 OF 8 USPATFULL on STN
91:54339 Method for eradicating infectious biological contaminants in body tissues.
Judy, Millard M., Dallas, TX, United States
Matthews, James L., Dallas, TX, United States
Newman, Joseph T., Dallas, TX, United States
Sogandares-Bernal, Franklin, Dallas, TX, United States
Baylor Research Foundation, Dallas, TX, United States (U.S. corporation)
US 5030200 19910709
APPLICATION: US 1989-433024 19891106 (7)
DOCUMENT TYPE: Utility; Granted.

CLM What is claimed is:

1. A method for eradicating infectious pathogenic biological contaminants from body fluid outside the body prior to introduction of the decontaminated body fluids into the body of a patient, said method comprising: admixing an effective, non-toxic amount of a photoactive compound with the body fluid to produce a resulting body fluid, the photoactive compound having an affinity to be selectively bound to the contaminants; maintaining the resulting body fluid in a suitable container in which there is no net mass transfer; and irradiating the resulting body fluid in the container with an effective level of essentially uniform intensity of radiation in the region of the visible spectrum, with a wavelength range of from about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the resulting fluid and exposes the photoactive-compound-bound contaminants to the radiation so as to eradicate such contaminants while maintaining

the viability of said body fluids to produce viable decontaminated body fluids.

2. The method as recited in claim 1 further comprising the step of selecting a body fluid from the group consisting of whole blood, blood plasma, serum, and fluids from plasmapheresis.

3. The method as recited in claim 1 further comprising the step of selecting a body fluid comprising of semen.

4. The method as recited in claim 1 further comprising the step of selecting a photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR2## said molecules with said formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the visible spectrum in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at at least approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecules having said molecular formula.

5. The method as recited in claim 4 wherein the amount of said mixture of porphyrins admixed with said fluid is from about 0.1 to about 50 micrograms per milliliter of body fluid.

6. The method as recited in claim 5 wherein the amount of said mixture of porphyrins admixed with said fluid is from about 2 to 50 micrograms per milliliter of body fluid.

7. The method as recited in claim 1 wherein the level of radiation is produced by a light source having a wavelength of from about 400 to about 1000 nm and an energy density of from about 0.1 to about 50 J/cm2.

8. The method as recited in claim 7 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density from about 1 to about 20 J/cm2.

9. The method as recited in claim 1 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising an envelope-containing virus.

10. The method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, Orthomyxoviridae, and Paramyxoviridae.

11. The method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

12. The method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

13. The method as recited in claim 12 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

14. The method as recited in claim 1 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

15. The method as recited in claim 1 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a Borrelia burgdorferi bacteria.

16. The method as recited in claim 1 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a malarial parasite.

17. The method as recited in claim 1 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a trypanosomal parasite.

18. The method as recited in claim 1 further comprising the step of agitating the resulting body fluid in the container.

19. The method as recited in claim 18 wherein the step of agitating is carried out by moving the container.

20. The method as recited in claim 18 wherein the step of agitating is carried out by the aid of an agitating means.

21. The method as recited in claim 20 wherein said agitating means comprises an agitating object.

22. The method as recited in claim 1 wherein said container is kept static.

23. A method for externally purifying a blood product to eradicate pathogenic biological contaminants selected from the group consisting of envelope-containing viruses, bacteria, malarial, and trypanosomal parasites prior to introduction of the decontaminated blood products intravenously into a patient, said method comprising: admixing an effective amount of a photoactive compound with the blood products to bind the contaminant with the photoactive compound, said photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR3## said molecules with said formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the visible spectrum in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at at least approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145 , 171.7 ppm relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecules having said molecular formula; maintaining the blood product containing the porphyrins-bound contaminants in a suitable container, exposable to a radiation source capable of irradiating the blood product and in which there is no net mass transfer; and irradiating the blood product in the container with an essentially

uniform intensity of radiation source in the region of visible spectrum, with a wavelength of from about 400 nm to about 1000 nm for an effective period of time to permit the radiation to penetrate through the blood product in the container and eradicate the contaminants while maintaining the viability of components in said blood product.

24. The method as recited in claim 23 wherein the amount of said mixture of porphyrins admixed with said blood product is from about 0.1 to about 50 micrograms per milliliter of blood product.

25. The method as recited in claim 24 wherein the amount of said mixture of porphyrins admixed with said blood product is from about 2 to about 50 micrograms per milliliter of blood product.

26. The method as recited in claim 23 wherein the level of radiation is produced by a light source having a wavelength of from about 400 to about 700 nm and an energy density of from about 0.1 to about 50 J/cm2.

27. The method as recited in claim 26 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density of from about 1 to about 20 J/cm2.

28. The method as recited in claim 23 further comprising the step of selecting blood product which contains pathogenic biological contaminants comprising an envelope-containing virus.

29. The method as recited in claim 28 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, Orthomyxoviridae, and Paramyxoviridae.

30. The method as recited in claim 28 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

31. The method as recited in claim 28 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

32. The method as recited in claim 31 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

33. The method as recited in claim 23 further comprising the step of selecting blood product which contains pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

34. The method as recited in claim 23 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a Borrelia burgdorferi bacteria.

35. The method as recited in claim 23 further comprising the step of selecting blood product which contains pathogenic biological contaminants comprising a malarial parasite.

36. The method as recited in claim 23 further comprising the step of selecting blood product which contains pathogenic biological contaminants comprising a trypanosomal parasite.

37. The method as recited in claim 23 further comprising the step of

agitating the resulting body fluid in the container.

38. The method as recited in claim 37 wherein the step of agitating is carried out by moving the container.

39. The method as recited in claim 37 wherein the step of agitating is carried out by the aid of an agitating means.

40. The method as recited in claim 39 wherein said agitating means comprises an agitating object.

41. The method as recited in claim 23 wherein said container is kept static.

42. A method for extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants said method comprising; removing blood from the body of a patient infected with infectious pathogenic biological contaminants; adding to said blood an effective, non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; maintaining said treated blood in a suitable container in which there is not net mass transfer; irradiating said contaminated blood admixed with photo-active compound in the container with an effective level of essentially uniform intensity of radiation in the region of visible spectrum, with a wavelength range of from about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of components in said blood to produce a viable and decontaminated blood; and returning said viable and decontaminated blood to the patient's body.

43. The method as recited in claim 42 further comprising the step of selecting a photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR4## said molecules with said formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the visible spectrum in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at at least approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecules having said molecular formula.

44. The method as recited in claim 43 further comprising the step of administering said mixture of porphyrins to the patient prior to the removal of the blood from the patient's body for irradiation.

45. The method as recited in claim 44 further comprising the step of administering said mixture of porphyrins to the patient between about thirty minutes and about one week prior to removal of the patient's blood for irradiation.

46. The method as recited in claim 44 further comprising the step of administering said mixture of porphyrins at a dosage from about 0.5 mg to about 40 mg per kg of body weight of the patient.

47. The method as recited in claim 42 further comprising the step of admixing said mixture of porphyrins with said blood in an amount from about 0.1 to about 50 micrograms per milliliter of said blood.

48. The method as recited in claim 47 further comprising the step of admixing said mixture of porphyrins with said blood in an amount from about 2 to about 50 micrograms per milliliter of said blood.

49. The method as recited in claim 42 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 1000 nm and an energy density of from about 1 to about 50 J/cm2.

50. The method as recited in claim 49 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density of from about 1 to about 20 J/cm2.

51. The method as recited in claim 42 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising an envelope-containing virus.

52. The method as recited in claim 51 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, Orthomyxoviridae, and Paramyxoviridae.

53. The method as recited in claim 51 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

54. The method as recited in claim 51 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

55. The method as recited in claim 54 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

56. The method as recited in claim 42 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

57. The method as recited in claim 42 further comprising the step of selecting body fluid which contains pathogenic biological contaminants comprising a Borrelia burgdorferi bacteria.

58. The method as recited in claim 42 further comprising the step of selecting the pathogenic biological contaminants comprising a malarial parasite.

59. The method as recited in claim 42 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising a trypanosomal parasite.

60. The method as recited in claim 42 further comprising the step of agitating the resulting body fluid in the container.

61. The method as recited in claim 60 wherein the step of agitating is carried out by moving the container.

62. The method as recited in claim 60 wherein the step of agitating is carried out by the aid of an agitating means.

63. The method as recited in claim 62 wherein said agitating means comprises an agitating object.

64. The method as recited in claim 42 wherein said container is kept static.

65. A method for extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants said method comprising: administering to the patient infected with infectious pathogenic foreign biological contaminants an effective, non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; waiting a period of time for the photoactive compound to be taken up by the blood; removing the blood from the body of the patient; maintaining the blood in a suitable container in which there is no net mass transfer; irradiating the blood admixed with photoactive compound in the container with an effective level of essentially uniform intensity of radiation in the region of visible spectrum, with a wavelength range of from about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of components in said blood to produce a viable and decontaminated blood; and returning the viable and decontaminated blood to the patient's body.

66. The method as recited in claim 65 wherein the waiting period of time is from about one hour to about one week.

L10 ANSWER 8 OF 8 USPATFULL on STN
89:90463 Method for eradicating infectious biological contaminants in body tissues.

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US 4878891 19891107
APPLICATION: US 1987-67237 19870625 (7)
DOCUMENT TYPE: Utility; Granted.

CLM What is claimed is:

1. A method for eradicating infectious pathogenic biological contaminants from body fluids outside the body prior to introduction of the decontaminated body fluids into the body of a patient, said method comprising: admixing an effective, non-toxic amount of a photoactive compound with the body fluid to produce a resulting body fluid, the photoactive compound having an affinity to be selectively bound to the contaminants; passing the resulting fluid under flow conditions through a cell assembly having a predetermined flow path; and irradiating the resulting fluid in the cell assembly as same passes through the flow path with an effective level of radiation in the region of the visible spectrum, with a wavelength range upwards of about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the resulting fluid and exposes the photoactive-compound-bound contaminants to the radiation so as to eradicate such contaminants while maintaining the viability of said body fluids to produce viable decontaminated body fluids.

2. The eradicating method as recited in claim 1 further comprising the

step of selecting a body fluid from the group consisting of whole blood, blood plasma, serum, and fluids from plasmapheresis.

3. The eradicating method as recited in claim 1 further comprising the step of selecting a body fluid comprising semen.

4. The eradicating method as recited in claim 1 further comprising the step of selecting a photoactive compound comprising a mixture of porphrins, at least a portion of the molecules of said porphrin mixture having the molecular formula: ##STR2## said molecules with said formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the ultraviolet and visible spectra in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm and possible 118 and 127 relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecule having said molecular formula.

5. The method of claim 4 wherein the amount of said mixture of porphyrins admixed with said fluids is from about 0.1 to about 50 micrograms per milliliter of body fluid.

6. The method of claim 5 wherein the amount of said mixture of porphyrins admixed with said fluids is from about 2 to 50 micrograms per milliliter of body fluid.

7. The method of claim 1 wherein the level of radiation is produced by a light source having a wavelength of from about 400 to about 1000 nm and an energy density of from about 0.1 to about 50 J/cm2.

8. The method of claim 7 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density from about 1 to about 20 J/cm2.

9. The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising an envelope-containing virus.

10. The eradicating method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, orthomyxoviridae, and Paramyxoviridae.

11. The eradicating method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

12. The eradicating method as recited in claim 9 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

13. The eradicating method as recited in claim 12 further comprising the step of selecting the Retrovirividae comprising a **human immunodeficiency virus**.

14. The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

15. The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising a malarial parasite.

16. The eradicating method as recited in claim 1 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising a trypanosomal parasite.

17. A method for externally purifying blood products to eradicate pathogenic biological contaminants selected from the group consisting of envelope-containing viruses, bacteria, malarial, and trypanosomal parasites prior to introduction of the decontaminated blood products intravenously into a patient, said method comprising: admixing an effective amount of a photoactive compound with the blood products to bind the contaminant with the photoactive compound, said photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR3## said molecules with said formula being fluorescent, phtosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the ultraviolet and visible spectra in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm and possible 118 and 127 relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecule having said molecular formula; passing the blood products containing the porphyrins-bound contaminants through a cell assembly having a flow path exposable to a radiation source capable of irradiating the blood products as same travels along the flow path; and irradiating the blood products with a radiation source in the region of visible spectrum, with a wavelength upwards of about 400 nm to about 1000 nm for an effective period of time to permit the radiation to penetrate through the blood products in the flow path of the cell assembly and eradicate the contaminants while maintaining the viability of components in said blood products.

18. The method of claim 17 wherein the amount of said mixture of porphyrins admixed with said blood products is from about 0.1 to about 50 micrograms per milliliter of blood products.

19. The method of claim 18 wherein the amount of said mixture of porphyrins admixed with said blood products is from about 2 to about 50 micrograms per milliliter of blood products.

20. The method of claim 17 wherein the level of radiation is produced by a light source having a wavelength of from about 400 to about 700 nm and an energy density of from about 0.1 to about 50 J/cm2.

21. The method of claim 20 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density of from about 1 to about 20 J/cm2.

22. The eradication method as recited in claim 17 further comprising the step of selecting blood products which contain pathogenic biological contaminants comprising an envelope-containing virus.

23. The eradicating method as recited in claim 22 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, Orthomyxoviridae, and Paramyxoviridae.

24. The eradicating method as recited in claim 22 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

25. The eradication method as recited in claim 22 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

26. The eradicating method as recited in claim 25 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

27. The eradicating method as recited in claim 17 further®r comprising the step of selecting blood products which contain pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

28. The eradicating method as recited in claim 17 further comprising the step of selecting body fluids which contain pathogenic biological contaminants comprising a malarial parasite.

29. The eradicating method as recited in claim 17 further comprising the step of selecting blood products which contain pathogenic biological contaminants comprising a trypanosomal parasite.

30. A method for eradicating infectious pathogenic biological contaminants from body tissues outside the body prior to transplanting the decontaminated body tissues onto the body of the patient, said method comprising: removing by excision from a donor a piece of human tissue that is translucent to light; admixing a effective, non-toxic amount of a photoactive compound with the body tissue suspended in a physiologically acceptabIe saline solution, the photoactive compound having an affinity to be selectively bound to the contaminants; and irradiating the resulting suspension of the body tissue gently a(g)gitated in a physiologically acceptable saline solution with an effective level of radiation in the region of the visible spectrum, with a wavelength range upwards of about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the body tissue and exposes the photoactive-compound-bound contaminants to the radiation so as to eradicate such contaminants while maintaining the viability of said body tissue to produce viable decontaminated body tissues suitable for transplantation.

31. The eradicating method as recited in claim 30 further comprising the step of selecting a body tissue from the group consisting of skin and cornea.

32. The eradicating method as recited in claim 30 further comprising the step of selecting a photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR4## said molecules with said

formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenic biological contaminants, forming a high molecular weight aggregate with absorption peaks in the ultraviolet and visible spectra in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm and possible 118 and 127 relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecule having said molecular formula.

33. The method of claim 30 wherein the level of radiation is produced by a light source having a wavelength of from about 400 to about 700 nm and an energy density of from about 0.1 to about 20 J/cm2.

34. The method of claim 33 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density from about 1 to about 20 J/cm2.

35. The eradicating method as recited in claim 30 further comprising the step of selecting body tissues which contain pathogenic biological contaminants comprising an envelope-containing virus.

36. The eradicating method as recited in claim 35 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviridae, Orthomyxoviridae, and Paramyxoviridae.

37. The eradicating method as recited in claim 35 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdovirdae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

38. The eradicating method as recited in claim 35 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

39. The eradicating method as recited in claim 38 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

40. The eradicating method as recited in claim 30 further comprising the step of selecting body tissues which contain pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

41. The eradicating method as recited in claim 30 further comprising the step of selecting body tissues which contain pathogenic biological contaminants comprising a malarial parasite.

42. The eradicating method as recited in claim 30 further comprising the step of selecting body tissues which contain pathogenic biological contaminants comprising a trypanosomal parasite.

43. A method for extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants said method comprising: removing blood from the body of a patient infected with infectious pathogenic biological contaminants; adding to said blood,

before the removal of the blood, an effective, non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; passing said treated blood through a cell assembly having a predetermined flow path; irradiating said contaminated blood admixed with photoactive compound in the cell assembly as same passes through the flow path with an effective level of radiation in the region of visible spectrum, with a wavelength range upwards of about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of components in said blood to produce a viable and decontaminated blood; and returning said viable and decontaminated blood to the patient's body.

44. The eradicating method as recited in claim 43 further comprising the step of selecting a photoactive compound comprising a mixture of porphyrins, at least a portion of the molecules of said porphyrin mixture having the molecular formula: ##STR5## said molecules with said formula being fluorescent, photosensitizing, having the capability of selectively binding to said pathogenicbiological contaminants, forming a high molecular weight aggregate with absorption peaks in the ultraviolet and visible spectra in water at approximately 365, 505, 537, 575, and 615 nanometers, absorption peaks in the infrared spectrum at approximately 3.0, 3.4, 6.4, 7.1, 8.1, 9.4, 12 and 15 microns, absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 9.0, 18.9, 24.7, 34.5, 62, 94.5, 130-145, 171.7 ppm and possible 118 and 127 relative to a 37.5 ppm resonance peak of dimethyl sulfoxide and additional absorption peaks in carbon-13 nuclear magnetic resonance study at approximately 27.9 ppm and 68.4 ppm relative to the resonance peak of tetramethylsilane in deuterated chloroform solvent; and at least 50 percent of the porphyrins in said mixture being of said molecule having said molecular formula.

45. The eradicating method as recited in claim 44 further comprising the step of administering said mixture of porphyrins to the patient prior to the removal of the blood from the patient's body for irradiation.

46. The eradicating method as recited in claim 45 further comprising the step of administering said mixture of porphyrins to the patient between about one hour and about one week prior to the removal of the patient's blood for irradiation.

47. The eradicating method as recited in claim 45 further comprising the step of administering said mixture of porphyrins at a dosage from about 0.5 mg to about 40 mg per kg of body weight of the patient.

48. The eradicating method as recited in claim 44 further comprising the step of admixing said mixture of porphyrins, dissolved in a physiologically acceptable saline solution, with the blood after said blood has been removed from the patient's body.

49. The eradicating method as recited in claim 48 further comprising the step of admixing said mixture of porphyrins with said blood in an amount from about 0.1 to about 50 micrograms per milliliter of said blood.

50. The eradicating method as recited in claim 49 further comprising the step of admixing said mixture of porphyrins with said blood in an amount from about 2 to about 50 micrograms per milliliter of said blood.

51. The method of claim 43 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 1000 nm and an energy density of from about 1 to about 50 J/cm2.

52. The method of claim 51 wherein the level of radiation is produced by a light source having a wavelength of from about 600 to about 700 nm and an energy density of from about 1 to about 20 J/cm2.

53. The eradicating method as recited in claim 43 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising an envelope-containing virus.

54. The eradicating method as recited in claim 53 further comprising the step of selecting the envelope-containing virus from the group consisting of Herpesviridae, Poxviridae, Iridoviridae, Hepadnaviriae, Orthomyxoviridae, and Paramyxoviridae.

55. The eradicating method as recited in claim 53 further comprising the step of selecting the envelope-containing virus from the group consisting of Rhabdoviridae, Bunyaviridae, Filoviridae, Nodaviridae, and Togaviridae.

56. The eradicating method as recited in claim 53 further comprising the step of selecting the envelope-containing virus from the group consisting of Flaviviridae, Retroviridae, and Arenaviridae.

57. The eradicating method as recited in claim 56 further comprising the step of selecting the Retroviridae comprising a **human immunodeficiency virus**.

58. The eradicating method as recited in cIaim 43 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising a bacteria selected from the group consisting of Streptococcus faecalis and Bacillus subtilis.

59. The eradicating method as recited in claim 43 further comprising the step of selecting the pathogenic biological contaminants comprising a malarial parasite.

60. The eradicating method as recited in claim 43 further comprising the step of selecting a blood which contains pathogenic biological contaminants comprising a trypanosomal parasite.

61. A method for extracorporeal treatment of the blood of a patient infected with infectious pathogenic biological contaminants said method comprising: removing blood from the body of a patient infected with infectious pathogenic foreign biological contaminants; adding to said blood, after the removal of the blood, an effective, non-toxic amount of photoactive compound having an affinity to be selectively bound to the infectious contaminants; passing said treated blood through a cell assembly having a pedetermined flow path; irradiating said contaminated blood admixed with photoactive compound in the cell assembly as the same passes through the flow path with an effective level of radiation in the region of visible spectrum, with a wavelength range upwards of about 400 nm to about 1000 nm, for an effective period of time such that the radiation penetrates the blood and exposes the photoactive-compound-bound infectious contaminants to the radiation so as to eradicate such infectious contaminants while maintaining the viability of compounds in said blood to produce a viable and decontaminated blood; and returning said viable and decontaminated blood to the patient's body.

62. The eradicating method as recited in claim 32 and further comprising the step of admixing said mixture of porphyrins, from about 0.1 to about 50 micrograms per milligram of body tissue, in a physiologically acceptable saline solution with said suspension of body tissue.

63. The eradicating method as recited in claim 62 and further comprising the step of admixing said mixture of porphyrins, from about 2 to 50 micrograms per milligram of body tissue, in a physiologically acceptable saline solution with said suspension of body tissue.

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=> file wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                20.29      48.79

FILE 'WPIDS' ENTERED AT 04:18:26 ON 02 OCT 2006
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=> d his

     (FILE 'HOME' ENTERED AT 04:11:15 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 04:11:30 ON 02 OCT 2006
                E RIOS ADAN/IN
L1            5 S E3
L2            5 S L1 AND (RT OR REVERSE TRANSCRIPTASE)

     FILE 'WPIDS' ENTERED AT 04:13:32 ON 02 OCT 2006
                E RIOS A/IN
L3           18 S E3-E11
L4            1 S L3 AND (RT OR REVERSE TRANSCRIPTASE)

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L5          259 S E3
L6            2 S L5 AND (RT OR REVERSE TRANSCRIPTASE)

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L7        47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L8          170 S L7 AND (PHOTOLABELING OR PHOTOINACTIVATION)
L9           83 S L8 AND AY<2000
L10           8 S L9 AND (REVERSE TRANSCRIPTASE)

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          5102 HUMAN IMMUNODEFICIENCY VIRUS
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L11      23476 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l11 and (photolabeling or photoinactivation)
             3 PHOTOLABELING
             7 PHOTOINACTIVATION
L12          0 L11 AND (PHOTOLABELING OR PHOTOINACTIVATION)

=> file medline
COST IN U.S. DOLLARS                              SINCE FILE       TOTAL
                                                       ENTRY     SESSION
FULL ESTIMATED COST                                     4.24       53.03

FILE 'MEDLINE' ENTERED AT 04:19:03 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

   http://www.nlm.nih.gov/mesh/
   http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
   http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
   http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (HIV or human immunodeficiency virus)
        163348 HIV
       1420903 HUMAN
        124822 IMMUNODEFICIENCY
        419508 VIRUS
         49412 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L13     168740 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l13 and (RT or reverse transcriptase)
        176484 RT
        161367 REVERSE
         86367 TRANSCRIPTASE
         86024 REVERSE TRANSCRIPTASE
                 (REVERSE(W)TRANSCRIPTASE)
L14      12183 L13 AND (RT OR REVERSE TRANSCRIPTASE)

=> s l14 and (photolabeling or photoinactivation)
           836 PHOTOLABELING
           674 PHOTOINACTIVATION
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L15 9 L14 AND (PHOTOLABELING OR PHOTOINACTIVATION)

=> d l15,cbib,ab,1-9

L15 ANSWER 1 OF 9 MEDLINE on STN
2004269420. PubMed ID: 15168794. Methylene blue **photoinactivation** of RNA viruses. Floyd Robert A; Schneider J Edward Jr; Dittmer Dirk P. (Oklahoma Medical Research Foundation, Auburn University, Auburn, AL 36849, USA.. robert-floyd@omrf.ouhsc.edu) . Antiviral research, (2004 Mar) Vol. 61, No. 3, pp. 141-51. Ref: 48. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB We present a review of the current status of the use of methylene blue (MB) **photoinactivation** of viruses starting with the first early observations up to its current use to inactivate **HIV**-1 in blood products. Basic mechanism of action studies conducted with model bacteriophages indicate that MB-photomediated viral RNA-protein crosslinkage is a primary lesion and that oxygen, specifically singlet oxygen, is very important also. Basic studies on the mechanism of action with **HIV** are lacking; however, we do show new data illustrating that viral **reverse transcriptase** inactivation per se cannot account for MB-mediated **photoinactivation**. We also show data illustrating that MB photomediates the inactivation of West Nile Virus, a flavivirus, which poses a significant new threat to the continental US. MB **photoinactivation** of viruses show significant promise because the technology not only offers significant potency but the history of safe MB use in human therapy makes it attractive also.

L15 ANSWER 2 OF 9 MEDLINE on STN
2002716478. PubMed ID: 12413867. Characterization of a binding site for template competitive inhibitors of **HIV**-1 **reverse transcriptase** using **photolabeling** derivatives. Lin Weiying; Li Ke; Doughty Michael B. (Department of Medicinal Chemistry, The University of Kansas, Lawrence, KS 66045, USA.) Bioorganic medicinal chemistry, (2002 Dec) Vol. 10, No. 12, pp. 4131-41. Journal code: 9413298. ISSN: 0968-0896. Pub. country: England: United Kingdom. Language: English.

AB Analogues of a novel class of template-competitive **reverse transcriptase** inhibitors (Li, K.; Lin, W.; Chong, K. H.; Moore, B. M.; Doughty, M. B. Bioorg. Med. Chem. 2002, 10, 507) were analyzed as photoprobes of **HIV**-1 **reverse transcriptase (RT)** heterodimer. The two photoprobes, 2-(4-azidophenacyl)thio-1,N(6)-etheno-2'-deoxyadenosine 5'-triphosphate 2 and the tetrafluoro analogue 2-(4-azido-2,3,5,6-tetrafluorophenacyl)thio-1,N(6)-etheno-2'-deoxyadenosine 5'-triphosphate 3, photodecomposed at 3500 A with half-lives of 4.0 and 2.5 min, respectively. Analysis of the photoproducts of 2m demonstrated that the etheno group is stable but the azido decomposes primarily to the 2-(S-[3H-diazepinon-4-yl]thio)-1,N(6)-etheno-dAMP. Photolysis of both 2 and 3 with **RT** resulted in a time-dependent loss of activity, with maximum inactivation of 83 and 60%, respectively. Both 2 and 3 showed concentration-dependent **photoinactivation** of **RT** in the concentration range from 0 to 100 microM, with EC(50)s of 20 and 25 microM and maximum inactivation of 80 and 60%, respectively. Both the time and concentration dependent **photoinactivation** were strongly protected by template-primer, but only poorly inhibited by even high concentrations of TTP. Radiolabeled analogues [beta,gamma-(32)P]-2 and [beta,gamma-(32)P]-3 photoincorporated into the p66 subunit, an incorporation also protected by template primer. Identification of the site of incorporation was problematic for both photoprobes, but evidence presented is consistent with labeling sites for the phenacyl side chains of both 2 and 3 in the template grip. Nevertheless, the **photoinactivation** and incorporation data are consistent with our earlier conclusions from the kinetic data that these inhibitors are specific for the free form of **RT** in competition with template/primer, and thus represent a novel class of

inhibitors.

L15 ANSWER 3 OF 9 MEDLINE on STN
2002106695. PubMed ID: 11814836. Template-competitive inhibitors of **HIV-1 reverse transcriptase**: design, synthesis and inhibitory activity. Li Ke; Lin Weiying; Chong Kar Hua; Moore Bob M; Doughty Michael B. (Department of Medicinal Chemistry, The University of Kansas, 1250 Wescoe Hall Drive, Lawrence, KS 66045, USA.) Bioorganic medicinal chemistry, (2002 Mar) Vol. 10, No. 3, pp. 507-15. Journal code: 9413298. ISSN: 0968-0896. Pub. country: England: United Kingdom. Language: English.

AB We report the design, synthesis and activity studies on a novel class of template-competitive **reverse transcriptase** inhibitors (TCRTIs). The TCRTIs are 1,N(6)-etheno analogues of a series of dATP-based template-competitive DNA polymerase inhibitors synthesized in our laboratory (Moore, B. M.; Jalluri, R.; Doughty, M.B. Biochemistry 1996, 35, 11634). Thus, nucleotides 2-(4-azidophenacyl)thio-1,N(6)-etheno-2'-deoxyadenosine 5'-triphosphate 1, the tetrafluoro analogue 2-(4-azido-2,3,5,6-tetrafluorophenacyl)thio-1,N(6)-etheno-2'-deoxyadenosine 5'-triphosphate 2 and its analogues were synthesized by alkylation of 2-thio-1,N(6)-etheno-2'-deoxyadenosine 5'-monophosphate with the corresponding chloro- or bromo-alkyl halides and converted to the triphosphate. Kinetically, nucleotides 1 and 2 are both competitive inhibitors of **reverse transcriptase** versus template/primer with K(i)'s of 8.0 and 7.4 microM, respectively, and non-competitive inhibitors versus TTP with K(i)'s of 15 and 10 microM, respectively. Nucleotide 3, which differs from 1 only in that it lacks the etheno group, non-complementary nucleotide triphosphates, and related monophosphates and nucleosides, are completely inactive as inhibitors of **reverse transcriptase** at concentrations up to 1 mM. **Photoinactivation** of **RT** by 1 was both time- and concentration-dependent, and protected by template/primer but not by dNTPs. The concentration-dependent inactivation data gave a K(D,app) of 17.2 microM and maximum inactivation of 90%, and radiolabeled [beta, gamma-32P]-1 photoincorporated specifically and covalently into the p66 subunit of **RT**. Thus the **photoinactivation** data support our main conclusion from the kinetic data that this class of **RT** inhibitors are non-substrate and template-competitive.

L15 ANSWER 4 OF 9 MEDLINE on STN
96355581. PubMed ID: 8702991. dNTP binding to **HIV-1 reverse transcriptase** and mammalian DNA polymerase beta as revealed by affinity labeling with a photoreactive dNTP analog. Lavrik O I; Prasad R; Beard W A; Safronov I V; Dobrikov M I; Srivastava D K; Shishkin G V; Wood T G; Wilson S H. (Novosibirsk Institute of Bioorganic Chemistry, Siberian Division of the Russian Academy of Sciences, 630090 Novosobirsk, Russia.) The Journal of biological chemistry, (1996 Sep 6) Vol. 271, No. 36, pp. 21891-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The dNTP binding pocket of **human immunodeficiency virus** type 1 **reverse transcriptase (RT)** and DNA polymerase beta (beta-pol) were labeled using a photoreactive analog of dCTP, exo-N-[beta-(p-azidotetrafluorobenzamido)-ethyl]-deoxycytidine-5'- triphosphate (FABdCTP). Two approaches of **photolabeling** were utilized. In one approach, photoreactive FABdCTP and radiolabeled primer-template were UV-irradiated in the presence of each enzyme and resulted in polymerase radiolabeling. In an alternate approach, FABdCTP was first UV-cross-linked to enzyme; subsequently, radiolabeled primer-template was added, and the enzyme-linked dCTP analog was incorporated onto the 3'-end of the radiolabeled primer. The results showed strong labeling of the p66 subunit of **RT**, with only minor labeling of p51. No difference in the intensity of cross-linking was observed with either approach. FABdCTP cross-linking was increased in the presence of a dideoxyterminated primer-template with **RT**, but not with beta-pol, suggesting a significant

influence of prior primer-template binding on dNTP binding for **RT**. Mutagenesis of beta-pol residues observed to interact with the incoming dNTP in the crystal structure of the ternary complex resulted in labeling consistent with kinetic characterization of these mutants and indicated specific labeling of the dNTP binding pocket.

L15 ANSWER 5 OF 9 MEDLINE on STN
96116204. PubMed ID: 8830122. Target structures for **HIV**-1 inactivation by methylene blue and light. Bachmann B; Knuver-Hopf J; Lambrecht B; Mohr H. (Blood Transfusion Service of the German Red Cross Lower Saxony, Institute Springe, Germany.) Journal of medical virology, (1995 Oct) Vol. 47, No. 2, pp. 172-8. Journal code: 7705876. ISSN: 0146-6615. Pub. country: United States. Language: English.

AB In a photodynamic virus inactivation procedure for human fresh frozen plasma the plasma is exposed to visible light in the presence of 1 microM methylene blue. This procedure is known to inactivate **HIV**-1 by at least 10(6.32) TCID50/ml within 10 minutes. To elucidate the mechanism of photodynamic inactivation of **HIV**-1 by methylene blue/light treatment, **reverse transcriptase (RT)**, the **HIV**-1 associated protein p24, and viral RNA were examined. In the dark, methylene blue up to 10 microM has no inhibitory effect on recombinant **RT**. In the presence of light, recombinant **RT** inactivation was dependent on illumination time and the concentration of methylene blue. After **photoinactivation** of the whole virus by methylene blue/light treatment, **RT** activity was also almost completely inhibited. Simultaneously, it was found by Western blotting that **HIV**-1 p24 and gp120 are altered in size, possibly due to protein cross-linking. In addition, it was shown by polymerase chain reaction (PCR) inhibition assay that **HIV**-1 inactivation leads to destruction of its RNA. In summary, methylene blue/light treatment acts on **HIV**-1 at different target sites: the envelope and core proteins, and the inner core structures RNA and **RT**.

L15 ANSWER 6 OF 9 MEDLINE on STN
95217901. PubMed ID: 7535561. Carboxanilide derivative non-nucleoside inhibitors of **HIV**-1 **reverse transcriptase** interact with different mechanistic forms of the enzyme. Fletcher R S; Syed K; Mithani S; Dmitrienko G I; Parniak M A. (Lady Davis Institute for Medical Research, Sir Mortimer B. Davis- Jewish General Hospital, Montreal, Quebec, Canada.) Biochemistry, (1995 Apr 4) Vol. 34, No. 13, pp. 4346-53. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Researchers at the National Cancer Institute first recognized the anti-**HIV** potential of the carboxanilide compound oxathiin carboxanilide (UC84) [Bader, J. P., et al. (1991) Proc. Natl. Acad. Sci. U.S.A. 88, 6740-6744]. We have compared the inhibitory effect of UC84 and a second-generation thiocarboxanilide derivative, UC38, on **HIV**-1 **reverse transcriptase (RT)** RNA-dependent DNA polymerase activity. UC38 was a much better inhibitor (IC50 = 0.8 microM) than UC84 (IC50 = 4.3 microM). Inhibition by UC84 was competitive with respect to primer/template (P/T), whereas that by UC38 was uncompetitive. Both compounds were mixed noncompetitive inhibitors with respect to deoxynucleoside triphosphate (dNTP). Both compounds protected **RT** from irreversible **photoinactivation** by an azido derivative of nevirapine, implying that UC84 and UC38 bind to the same region of **RT** as nevirapine. UC84 photoprotected both free **RT** and the **RT**-P/T binary complex, but did not protect the **RT**-P/T-dNTP ternary complex. In contrast, UC38 completely photoprotected the **RT**-P/T-dNTP ternary complex, but not free **RT** or the **RT**-P/T binary complex. UC84 and UC38 thus appear to bind to different mechanistic forms of **RT** in the polymerase reaction sequence.

L15 ANSWER 7 OF 9 MEDLINE on STN
94340163. PubMed ID: 7520331. **Photolabeling** of the enzymes of the 2-5A synthetase/RNase L/p68 kinase antiviral systems with azido probes.

Suhadolnik R J. (Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA 19140.) Progress in molecular and subcellular biology, (1994) Vol. 14, pp. 260-75. Ref: 77. Journal code: 0233223. ISSN: 0079-6484. Pub. country: United States. Language: English.

L15 ANSWER 8 OF 9 MEDLINE on STN
91368342. PubMed ID: 1716385. Preliminary studies of **photoinactivation** of **human immunodeficiency virus** in blood. Matthews J L; Sogandares-Bernal F; Judy M M; Marengo-Rowe A J; Leveson J E; Skiles H; Newman J T; Chanh T C. (Baylor Research Foundation, Southern Methodist University, Dallas, Texas.) Transfusion, (1991 Sep) Vol. 31, No. 7, pp. 636-41. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB The transmission of **human immunodeficiency virus** (**HIV**) by blood or blood components is a major concern in blood banking. A photodynamic flow cell system was designed to inactivate cell-free **HIV** mixed with blood from a healthy donor. Blood containing 4 x 10(3) infectious units of **HIV** was treated with 10 and 20 micrograms per mL of commercially available dihematoporphyrin ether (DHE) per mL. Aliquots of this mixture were then held in the dark or irradiated in a flow cell illuminated at a light energy density of 5 J per cm2 provided by a xenon light source equipped with a 630 +/- 5 nm band-pass interference filter; the aliquots were subsequently placed in A.301 cells. All infected cultures were assessed for **reverse transcriptase** (**RT**) activity for 17 days. **RT** activity for either concentration of dye was significantly reduced in irradiated samples as compared to that in samples held in the dark. Blood samples from volunteers also were assessed for the effects of the inactivation process on red cells at concentrations of DHE up to 200 micrograms per mL. No effects were observed on red cell 2,3 DPG or ATP, whole blood potassium concentrations, red cell osmotic fragility, or blood cell antigens.

L15 ANSWER 9 OF 9 MEDLINE on STN
91152012. PubMed ID: 1705436. A novel dipyridodiazepinone inhibitor of **HIV**-1 **reverse transcriptase** acts through a nonsubstrate binding site. Wu J C; Warren T C; Adams J; Proudfoot J; Skiles J; Raghavan P; Perry C; Potocki I; Farina P R; Grob P M. (Department of Biochemistry, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877.) Biochemistry, (1991 Feb 26) Vol. 30, No. 8, pp. 2022-6. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB A novel dipyridodiazepinone, 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]- [1,4]diazepin-6-one (BI-RG-587), is a selective noncompetitive inhibitor of **HIV**-1 **reverse transcriptase** (**RT**-1). An azido photoaffinity analogue of BI-RG-587 was synthesized and found to irreversibly inhibit the enzyme upon UV irradiation. BI-RG-587 and close structural analogues competitively protected **RT**-1 from inactivation by the photoaffinity label. A thiobenzimidazolone (TIBO) derivative, a nonnucleoside inhibitor of **RT**-1, also protected the enzyme from **photoinactivation**, which suggests a common binding site for these compounds. Substrates dGTP, template-primer, and tRNA afforded no protection from enzyme inactivation. A tritiated photoaffinity probe was found to stoichiometrically and selectively label p66 such that 1 mol of probe inactivates 1 mol of **RT**-1.

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L4              1 S L3 AND (RT OR REVERSE TRANSCRIPTASE)

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L6              2 S L5 AND (RT OR REVERSE TRANSCRIPTASE)

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L10             8 S L9 AND (REVERSE TRANSCRIPTASE)

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L15             9 S L14 AND (PHOTOLABELING OR PHOTOINACTIVATION)

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